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Original article

Depression Over Psoriasis: Assessment of associated Relief by addition of ADalimumab for the treatment of Psoriasis: Observational study (DORADO - Ps)

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Abstract

Background: Psoriasis is associated with a variety of psychological difficulties, including poor self-esteem, sexual dysfunction, anxiety, depression, and suicidal ideation.

Objectives: The aim of this study was to obtain further data on the extent of depression among psoriatic patients, the effectiveness of adalimumab treatment on the depression symptoms associated with psoriasis and to explore the association between improvement in depression symptoms and improvement in Psoriasis Area and Severity Index.

Methods: The effects of adalimumab (40 mg every other week) on ZDS score and PASI at week 24 were assessed. Relationships between ZDS and PASI were assessed. Changes in ZDS score were compared for patients with and without a 75% or greater reduction in baseline PASI score. An improvement of 6 points or more in the Zung depression scale was considered a clinically meaningful improvement.

Results: Forty five Patients with moderate to severe psoriasis were assessed for depression symptoms at baseline and week 24 using the Zung Self-rating Depression Scale (ZDS). At month 6 after starting adalimumab, 80% of enrolled patients achieved 75% improvement in their PASI score (PASI75) at month 6 of adalimumab therapy and 97.8% achieved a meaningful improvement of Zung depression score (more than 6 points decline in the Zung depression score). Age at time of assessment significantly predicted depression ($p = 0^{*}030$), with the younger age predicting a higher depression score (standard co-efficient -.451). Achieving PASI 75 could significantly predict improvement in depression ($p = 0.002$, standard coefficient-.746).

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Conclusion: Adalimumab may be associated with relief symptoms of depression in patients with moderate to severe psoriasis. Reductions in depression symptoms were significantly correlated with reductions in psoriasis severity.
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Keywords: Psoriasis; Adalimumab; Depression

1. Introduction

Psoriasis is a common chronic condition that affects 1–3% of the general population and estimates suggest that 0.4–2.3% of the adult population have psoriasis but remain undiagnosed (Kurd and Gelfand, 2003).

Psoriasis is associated with a variety of psychological difficulties, including poor self-esteem, sexual dysfunction, anxiety, depression, and suicidal ideation. Psoriasis is associated with substantial impairment of health-related quality of life (HRQOL), negatively impacting psychological, vocational, social, and physical functioning (Skevington et al., 2006). The psychiatric morbidity in psoriasis may be primary or secondary to the impact of the disease upon the patient's quality of life. The psychological and psychiatric morbidity in psoriasis is often a more important indicator of the disability experienced by the patient than the dermatologic aspects of the disorder (Kirkby et al., 2001). Psoriasis-related stress has been associated with greater psychiatric morbidity (Fortune et al., 1997). A wide range of psychological characteristics have been reported in various cross sectional surveys including high depression/anxiety scores, obsessionality, and difficulties with verbal expression of emotions, especially anger, social stigmatization, high stress levels, physical limitations, depression, employment problems and other psychosocial comorbidities experienced by patients with psoriasis are not always proportional to, or predicted by, other measurements of disease severity, such as body surface area involvement or plaque severity (Gupta et al., 1987).

Relatively high rates of depression are reported in patients with psoriasis (Bouguéon and Misery, 2008; Van Voorhees and Fried, 2009). Studies found notably higher degrees of depression in patients with psoriasis than controls (Hardy and Cotterill, 1982). In another study, 35 of 76 (46%) study patients claimed that they were "often" or "always" depressed (Devrimci-Ozguven et al., 2000) because of their condition. In the Akay et al. (2002) study depression rate was 58% in the patients with psoriasis and 53% in the patients with lichen planus, while it was 20% in the control group.

Tumor necrosis factor (TNF), α proinflammatory cytokine, has been implicated in the pathogenesis of both psoriasis and depression (Chodorowska, 1998; Haack et al., 1999; Gupta and Gupta, 2003). Patients with psoriasis have elevated concentrations of TNF in skin and serum samples, and a direct correlation exists between TNF concentrations and psoriasis symptoms as measured by Psoriasis Area and Severity Index (PASI) scores Mussi et al., 1997.

Significantly elevated concentrations of TNF have been observed in the plasma of patients with acute depression and in patients with major depression who are resistant to therapy for depression. These findings suggest that inhibition of inflammatory cytokines in patients with depression may improve depression symptoms (Himmerich et al., 2008).

Adalimumab is a fully human monoclonal IgG1 antibody against TNF that has demonstrated efficacy and safety in the treatment of moderate to severe psoriasis. In addition to reducing the physical symptoms of psoriasis, adalimumab has been shown to improve dermatology-specific and general mental and physical HRQOL to levels comparable with that of the general population (Revicki et al., 2008).

2. Study objective(s)

The objective of this study was to assess changes in the depression symptoms in patients with psoriasis before and after the addition of adalimumab therapy using Zung Depression Scale Zung (1970), also to assess the correlation between improvement in depression symptoms and other factors such as age, gender, disease duration, BMI & improvement in PASI in patients are included in the study.

3. Methods and patients

This was a post-registration, observational, surveillance, prospective, non-comparative study that was conducted in Saudi Arabia with a total of 45 patients. The study protocol was restricted to patients fulfilling the following search criteria: (i) patient's age >18 years, (ii) with moderate to severe chronic plaque psoriasis, (iii) with a degree of depression, as measured by Zung Self-rating Depression Scale (ZDS) (50 points or more) and (iv) with no contraindications or objections to receive adalimumab treatment. Patients on anti-depressant therapy for a period of less than 6 months at the time of inclusion in the study were excluded.

The study was approved by local Clinical Research Ethics Committees and was carried out in accordance with the principles contained in the Declaration of Helsinki. Written informed consent was obtained from every subject prior to study entry.

Patients received treatment with adalimumab according to the prescribed drug information detailed in the summary of product characteristics and physicians' clinical practice. The initial dose was 40 mg every other week, any changes

in the dose was left to the physician's judgment but was recorded in the study follow up sheets. Each patient was observed for a period of maximum 6 months, if the patient withdrew within the period of 6 months of follow-up then the results of the last follow-up visit would be used for result analysis.

Demographic and baseline clinical data were collected at patient enrollment, including PASI, ZDS and the use of concomitant medications. Before treatment, a chest X-ray and a tuberculin skin test (TST) with protein-purified derivative were performed to rule out latent tuberculosis. Follow-up data (physical examination, vital signs and laboratory tests, disease activity, observed AEs, and concomitant used drugs) were collected in every follow up visit.

Treatment effectiveness in skin manifestations was evaluated in terms of PASI, ranging from 0 to 72. PASI 75 was calculated based on patients showing $\geqslant$75% improvement in their PASI scores. Depression status was evaluated in terms of ZDS, with a score between 25 and 49 points interpreted as no depression, mild depression is between 50 and 59 points, moderate depression is between 60 and 69 points and severe depression is $\geqslant$70 points. An improvement of 6 points or more in the Zung depression scale was considered a clinically meaningful improvement.

4. Statistical analysis

This is an observational study conducted during the period from September 2012 to April 2013 in three centers.

Continuous variables were described using the mean, median and standard deviation, whereas categorical variables were described by their absolute and relative frequencies. Safety was evaluated regarding occurrence of AEs and changes in laboratory values in all patients were included in the study; this sample was also used for the description of baseline characteristics. Efficacy analysis was performed on the intent-to-treat population, defined as all patients included in the study, using a visit-wise approach. For the primary efficacy variables, missing final data were imputed using last observation carried forward (LOCF). All tests were 2-sided and the 0.05 level was used as the cut off value for statistical significance and the following statistical measures were used. All analyses were performed using the SPSS statistical software, version 15.0 (SPSS Inc., Chicago, IL, USA).

5. Results

Of the 51 patients with a diagnosis of moderate-to-severe plaque psoriasis screened for DORADO-Ps, 45 (88%) gave consent to participate in the study. At month 6, 100% of the enrolled patients completed the study. Overall, 44.4% of patients enrolled were females while 55.6% were males, and 97.8% were Saudis. They had a mean age of 37.36 years (range 21–70 years), and their mean disease duration was 5.4 years (range 1–24 years); 22% of the patients enrolled suffered of psoriatic arthritis (PsA), and 80% had a body mass index (BMI) of more than 25.

At baseline, the enrolled patients had a mean PASI score of 15.17 points, and a mean Zung depression score of 60.84 points (range 50–76). 46.7%, 33.3% and 20% of patients suffered of mild, moderate and severe depression respectively.

After baseline assessment and collecting consent all patients were screened for tuberculosis and infection then administered a loading dose of adalimumab (80 mg subcutaneously); 64.4% of patients were on concomitant medications at the time of first administration of adalimumab, more details about concomitant medications are present in Table 1.

At month 6 after starting adalimumab, Mean PASI score of enrolled patients was significantly reduced from 15.17 at baseline to 3.32 at month 6 ($p < 0.0001$), and the mean Zung depression score was significantly reduced from 60.84 to 35.29 ($p < 0.0001$) (Figure 1). 80% of enrolled patients achieved $\geqslant$75% improvement in their PASI score (PASI75) at month 6 of adalimumab therapy and 97.8% achieved a meaningful improvement of the Zung depression score (more than 6 points decline in the Zung depression score). At the end of the study, 9% of enrolled patients had mild depression, while 92% showed no depression (Zung score < 49 points).

Compliance rate for adalimumab therapy was 87.8%, measured by comparing the number of doses planned for

Table 1
Patients on concomitant medications.*

Concomitant medications	*N* (%)
No	16 (35.6)
Steroids	14 (31.1)
Emollients	25 (55.6)
Keratolytics	7 (15.6)
Phototherapy	4 (8.9)
Methotrexate	2 (4.4)
Calcipotriol	1 (2.2)

* 20 Patients were on more than one concomitant medication.

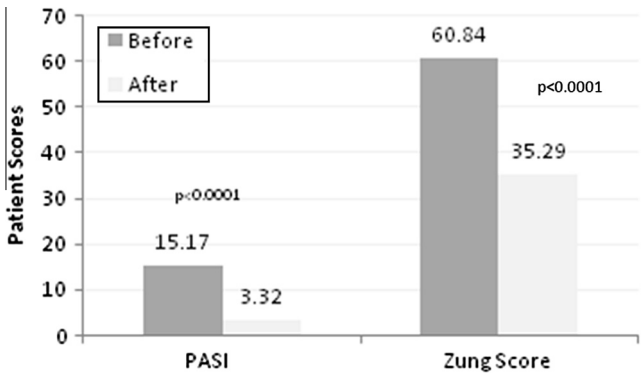

Figure 1. PASI and Zung depression scores – response to adalimumab therapy.

administration during the 6 months versus the number of doses actually administered during the same period. There was no withdrawal from the study at the end of 6 months.

One patient suffered from gastrointestinal disorders while another patient developed respiratory tract infection during the duration of the study; both were managed and continued their treatment regimen.

Regression analyses were conducted to determine predictors of depression in the patients enrolled in the study. Age at the time of assessment significantly predicted depression ($p = 0{\cdot}030$), with the younger age predicting a higher depression score (standard co-efficient −.451). Achieving PASI 75 could significantly predict improvement in depression ($p = 0.002$, standard co-efficient −.746). Gender, race, BMI, disease duration and the presence of psoriatic arthritis all could not significantly predict depression severity. Our study did not show significant difference in results between patients with concomitant medications and those without concomitant medications.

6. Discussion

The effective treatment of psoriasis has been found to improve symptoms of depression associated with the condition (Fortune et al., 2004).

Our patients were assessed for depression symptoms using the Zung Self-rating Depression Scale (ZDS). It has the advantage of acceptable reliability and being available in the public domain. *It was* developed as a short, simple and quantitative self-report measure of depression. The scale attempts to include all of the symptoms of depression. The items aim to penetrate the affective, behavioral, cognitive and physiological aspects of depression. The items were selected on the basis of the diagnostic criteria for depression and factor analytic studies.

Our study incorporated classic depression assessment instruments to examine an important question: does a known effective treatment for the clinical symptoms of plaque psoriasis improve symptoms of psoriasis-associated depression, which are conjectured to involve a cytokine that is closely involved in the disease process of psoriasis? We found that symptoms of depression were significantly improved with adalimumab. Related findings have been previously reported with adalimumab (Menter, 2010) and etanercept (Tyring et al., 2006) suggesting that anti-TNFα therapies such as a class can reduce depression in patients with psoriasis.

During the 24-week treatment period, however, reductions in depression symptoms were significantly correlated with reductions in psoriasis severity.

PASI 75 responders experienced a significantly greater improvement in depression symptoms than non responders.

This result is consistent with that of Mentor et al. Menter (2010), but inconsistent with the results of Tyring et al. (2006) who failed to detect strong correlation between PASI and depression improvement.

During the last 10 years, it has been established that pro-inflammatory cytokines such as interleukin-1 (IL-1), IL-6 and TNF-α induce true major depressive disorders in physically ill patients with no previous history of mental disorders (Dantzer et al., 2008). For example, TNF-α has been found to increase in depressed female patients when compared with healthy women (Kahl et al., 2006). And it was hypothesized that these immune alterations associated with depression may contribute to the pathophysiologic processes of the associated disorders e.g. osteoporosis, dyslipidemia and diabetes and psoriasis (Kahl et al., 2005).

Three different mechanisms might link the activation of the cytokine system, of which TNF-α is a part, to the pathophysiology of depression. At first, as proinflammatory cytokines and serotonergic homeostasis have both been implicated in the pathophysiology of major psychiatric disorders, various authors hypothesized that cytokines might also activate neuronal serotonin transporter. This idea would underline the theory of a serotonin deficiency during depression and the pharmacodynamic mechanism of selective serotonin reuptake inhibitors (SSRI) in the treatment of depression, because SSRIs lead to recovery from depression via deactivation of serotonin transporters (Pickering et al., 2005). Zhu et al. found TNF-α stimulated serotonin uptake in both a rat embryonic raphe cell line and in mouse midbrain and striatal synaptosomes. These results provided evidence that proinflammatory cytokines can acutely regulate neuronal serotonin transporter activity (Zhu et al., 2006).

Second, immune activation with increased production of pro-inflammatory cytokines activates the tryptophan- and serotonin-degrading enzyme indolamine-2,3-dioxygenase (IDO) Wichers and Maes, 2002.

Third, it has been postulated that the activation of the cytokine system might play a causative role in the depression related activation of the hypothalamic pituitary axis system (O'Brien et al., 2004; Schöbitz et al., 1994; Silverman et al., 2005).

However, the role of the soluble TNF-α receptors p55 and p75 (sTNF-R p55 and p75) has not been investigated so far in patients with depressive disorder. One single study in patients with heart failure found elevated sTNF-R p55 levels associated with a higher risk for depression (Moorman et al., 2007).

Langley et al., observed significant improvement in anxiety and depression scores in patients treated with ustekinumab, with significant correlation between improvement in PASI score and improvement in anxiety and depression score (Langley et al., 2010).

These findings suggest that inhibition of inflammatory cytokines in patients with depression may improve depression symptoms, but further studies are needed to address this question. Although psoriasis is an inflammatory disease mediated by TNF, it is unclear to what degree depression in psoriasis is TNF mediated versus a consequence of other psoriasis symptoms. The results of this analysis

cannot distinguish whether adalimumab has a direct or indirect effect on depression.

Alternatively, the presence of a strong correlation between PASI and depression improvement after treatment with both adalimumab and ustekinumab could indicate that treatment affected severity of depression indirectly.

However, the study was not designed to detect any effect of treatment with adalimumab on primary depression.

The psychological effects of psoriasis are not strictly determined by the severity of skin manifestations: environmental, cognitive, and life-event factors might all interact to perpetuate depression despite improvements in skin disease.

The fairly short treatment period during which depression data were collected (24 weeks) may have limited our findings; therefore, additional long-term studies would be useful in further elucidating the long-term impact of adalimumab on anxiety and depression in patients with moderate-to-severe psoriasis.

A broader concept of depression in the context of psoriasis will permit consideration of the usefulness of pharmacological and biopsychosocial approaches in the management of this complex condition. Thus, this study represents an important advancement in knowledge about psoriasis and the symptoms of depression, and the relation between them.

7. Conclusion

Adalimumab relieves symptoms of depression in patients with moderate to severe psoriasis. There was a significant correlation between reduction in depression symptoms and the improvement in psoriasis severity, age at the onset of disease was the only other factor that is correlated with improvement in depression. The high prevalence of depression among patients included in this study suggests that screening for depression symptoms should be incorporated into dermatology practice as a part of the management of psoriasis.

Disclosure

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